EDITORIAL

Darwin and the survival of the fittest in modern interventional cardiology

V K Bhatia, C Di Mario

Heart 2006;**92**:1017–1018. doi: 10.1136/hrt.2005.083923

The diabetic patient requires a full armamentarium of proven and developing treatments in order to minimise periprocedural risk as well as improve long term outcome

The use and disuse of new drugs, devices and treatments follows a frantic pace in interventional cardiology. A taste for innovation is probably a necessary inborn trait that may ''naturally select'' individuals who successfully pursue a career in interventional cardiology. In a healthcare environment with limited resources the competition between new and old treatments resembles the Darwinian ''struggle for survival''. However, the dark side of this Darwinian marker of success is the attitude of the interventionalist to forget too hastily the proven benefits of established treatments when their attention is distracted by newly emerging therapies.

DIABETES CONFERS HIGHER RISK FOR PCI

Diabetes mellitus portends a worse prognosis in patients with coronary artery disease who undergo either percutaneous coronary intervention (PCI) or surgical revascularisation.[1 2] The pathophysiology for the higher complication rate found in diabetic patients may involve an enhanced platelet activation state[3] and proliferative response[4] resulting in an elevated risk of thrombosis, embolisation and re-stenosis.[2 5]

Platelet glycoprotein (Gp) IIb/IIIa inhibitors are potent antiplatelet agents and pooled analysis of earlier studies have shown they confer sustained mortality benefit in diabetic patients undergoing plain balloon angioplasty or percutaneous bare metal stent implantation (PCI).[6]

The recent trials of drug eluting stents (DES) have shown a significant fall in target vessel revascularisation rates, but they have failed thus far to show any clear mortality benefit in diabetic patients.[7 8] One may argue that the characteristics of the population treated in these initial trials, including mainly patients with single vessel disease and a good ejection fraction, may have undermined the potential benefit of DES. Restenosis may conceivably have deadly consequences in patients with multivessel or left main stem disease who have silent ischaemia and accelerated disease progression in untreated segments.

BENEFITS OF GLYCOPROTEIN IIB/IIIA INHIBITORS IN DIABETIC PATIENTS RECEIVING DES

In this issue of Heart, Goncalves *et al*[9] remind us of an obvious truth: the benefit conferred by a new treatment does not cancel the effectiveness of a pre-existing proven therapy if the two treatments have completely different operative mechanisms. In a relatively large cohort of 203 patients receiving sirolimus eluting stents, the use of Gp IIb/IIIa inhibitors led to a reduction of death and non-fatal myocardial infarction (MI) (from 12.1 to 4.8 at one year) that was greater than that observed with Gp IIb/IIIa inhibitors in the seminal trials of plain balloon angioplasty and bare metal stents.[6] In a real world population with complex coronary disease (average stent length of 42.6 mm in the treated group) it may be hypothesised that prompt inhibition of platelet function reduces platelet plugging at the ostia of multiple side branches covered by stents and prevents distal embolisation, these being the main causes of periprocedural damage during stent implantation. As the use of longer stents is a consequence of the strategy of full plaque coverage adopted with DES, one may postulate that the advantages of Gp IIb/IIIa inhibitors are likely to be greater now than before.

LIMITATIONS OF THE STUDY

It is more difficult to explain another striking result from this study—the finding that at one year the curves of the two randomisation arms for major adverse cardiac events (MACE)-free and death or MI-free survival continue to separate. Although one can foresee a reduced late mortality rate from the initial fall of non-Q wave infarction, it would be difficult to understand why the effect on MI would continue long term. Since this is a non-randomised study, any difference in the observed outcome can be significantly influenced by differences in the baseline clinical, angiographic and procedural characteristics driven by the selection process of candidates for Gp IIb/IIIa inhibitors. Although not reaching statistical significance, there was a noticeable trend of greater unfavourable variables stacked against the group not receiving the Gp IIb/IIIa inhibitors (for example, greater percentage of patients with previous MI, coronary artery bypass surgery and peripheral arterial disease).

Abbreviations: DES, drug eluting stents; Gp, glycoprotein; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target lesion revascularisation

See end of article for authors' affiliations

Correspondence to: Professor Carlo Di Mario, Department of Interventional Cardiology, The Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; c.dimario@rbh.nthames.nhs.uk

Published Online First 31 January 2006

Various mechanism(s) have been proposed to explain the reduced target lesion revascularisation (TLR) rates observed with Gp IIb/IIIa inhibitors in some of the aforementioned studies. These include cross-reaction with the leucocyte integrin Mac-1[10] and also blocking vitronectin ($\alpha_v\beta_3$) receptors on platelets and smooth muscle cells,[11] thereby limiting neointimal hyperplasia.[12] However, no randomised comparisons have confirmed these observations, and the results of this study suggest that such effects of Gp IIb/IIIa inhibitors persist and cause an additional positive response even in the presence of high local concentrations of an antiproliferative agent (sirolimus) in the stent.

Another limitation of the study by Goncalves *et al*[9] involved the timing and dose of clopidogrel in relation to the procedure. Recent studies have demonstrated that an aggressive pre-PCI regimen of aspirin and 600 mg clopidogrel leads to no significant additional benefit of Gp IIb/IIIa inhibitor on risk of death or MI in diabetic patients receiving mainly bare metal stents.[13 14] This issue becomes all the more pertinent when it was subsequently disclosed that the two insulin-requiring diabetics who suffered thrombotic complications had an insufficient loading regimen of 300 mg clopidogrel apparently given immediately after the procedure.

FUTURE DIRECTIONS

Clopidogrel with a high loading dose of 600 mg is now being tested by the Munich group in a new randomised trial of unstable patients, but this drug, unlike Gp IIb/IIIa inhibitors, induces no more than 80% inhibition of platelet aggregation with a slow onset of action and a large variability in response. As developments in peri-PCI adjuvant drug treatment evolve, newer safer agents may threaten to supersede the use of Gp IIb/IIIa inhibitors. Another drug which may reduce the need for Gp IIb/IIIa inhibitors is the direct anti-thrombin bivalirudin which, unlike heparin, does not induce platelet activation. In a recent study with stable or mildly unstable patients undergoing PCI, bivalirudin was as effective as heparin and Gp IIb/IIIa inhibitors with lower bleeding, vascular complication rates and shorter intensive therapy unit stay.[15] Bivalirudin is now under evaluation in a trial of highly unstable patients with a complex randomisation scheme.[16]

While awaiting the results of such trials, this study reminds us all that the diabetic patient requires a full armamentarium of proven and developing treatments in order to minimise periprocedural risk as well as improve long term outcome.

Authors' affiliations
V K Bhatia, C D Mario, Department of Interventional Cardiology, The Royal Brompton Hospital, London, UK

Conflict of interest: none.

REFERENCES

1 **Barsness GW**, Peterson ED, Ohman EM, *et al*. Relationship between diabetes mellitus and long-term survival after coronary bypass and angioplasty. *Circulation* 1997;**96**:2551–6.
2 **Stein B**, Weintraub WS, Gebhart SP, *et al*. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. *Circulation* 1995;**91**:979–89.
3 **Ferroni P**, Basili S, Falco A, *et al*. Platelet activation in type 2 diabetes mellitus. *J Thromb Haemost* 2004;**2**:1282–91.
4 **Aronson D**, Bloomgarden Z, Rayfield EJ. Potential mechanisms promoting restenosis in diabetic patients. *J Am Coll Cardiol* 1996;**27**:528–35.
5 **Tang WH**, Lincoff AM. Diabetes, coronary intervention, and platelet glycoprotein IIb/IIIa blockade: the triad revisited. *Circulation* 2004;**110**:3618–20.
6 **Bhatt DL**, Marso SP, Lincoff AM, *et al*. Abciximab reduces mortality in diabetics following percutaneous coronary intervention. *J Am Coll Cardiol* 2000;**35**:922–8.
7 **Hermiller JB**, Raizner A, Cannon L, *et al*. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. *J Am Coll Cardiol* 2005;**19**:1172–9.
8 **Moussa I**, Leon MB, Baim DS, *et al*. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (sirolimus-coated Bx velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. *Circulation* 2004;**109**:2273–8.
9 **de Araujo Goncalves P**, Seabra-Gomes R, Teles R, *et al*. Complementary effects of sirolimus-eluting stents and glycoprotein IIb/IIIa inhibitors for percutaneous coronary intervention in diabetic patients: one-year follow-up of a single-centre registry. *Heart* 2006;**92**:1155–6.
10 **Simon DI**, Xu H, Ortlepp S, *et al*. 7E3 monoclonal antibody directed against the platelet glycoprotein IIb/IIIa cross-reacts with the leukocyte integrin Mac-1 and blocks adhesion to fibrinogen and ICAM-1. *Arterioscler Thromb Vasc Biol* 1997;**17**:528–35.
11 **Tam SH**, Sassoli PM, Jordan RE, *et al*. Abciximab (ReoPro, chimeric 7E3 Fab) demonstrates equivalent affinity and functional blockade of glycoprotein IIb/IIIa and alpha(v)beta3 integrins. *Circulation* 1998;**98**:1085–91.
12 **Srivatsa SS**, Fitzpatrick LA, Tsao PW, *et al*. Selective alpha v beta 3 integrin blockade potently limits neointimal hyperplasia and lumen stenosis following deep coronary arterial stent injury: evidence for the functional importance of integrin alpha v beta 3 and osteopontin expression during neointima formation. *Cardiovasc Res* 1997;**36**:408–28.
13 **Mehilli J**, Kastrati A, Schuhlen H, *et al*. Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. *Circulation* 2004;**110**:3627–35.
14 **Kastrati A**, Mehilli J, Schuhlen H, *et al*. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 2004;**350**:232–8.
15 **Rha SW**, Kuchulakanti PK, Pakala R, *et al*. Bivalirudin versus heparin as an antithrombotic agent in patients treated with a sirolimus-eluting stent. *Am J Cardiol* 2004;**94**:1047–50.
16 **Stone GW**, Bertrand M, Colombo A, *et al*. Acute catheterization and urgent intervention triage strategy (ACUITY) trial: study design and rationale. *Am Heart J* 2004;**148**:764–75.